THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAYMOND W. KOSLEY JR., LARRY DAVIS
and VERONICA TABERNA

Appeal No. 1997-2182
Application 08/137,443[1]

ON BRIEF

Before WINTERS, W. SMITH and METZ, ***Administrative Patent Judges***.

METZ, ***Administrative Patent Judge***.

DECISION ON APPEAL

This is an appeal from the examiner's refusal to allow claims 1 through 22, all the claims remaining in this application.

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[1] Application for patent filed October 15, 1993.

THE INVENTION

The appealed subject matter is directed to a genus of compounds which may be broadly characterized as galanthamine derivatives, a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an acetylcholinesterase (AChE) inhibiting amount of the galanthamine derivative and a method of treating memory dysfunction characterized by decreased cholinergic function by administering to a mammal an AChE inhibiting amount of the galanthamine derivative. According to appellants, the claimed family of galanthamine derivatives possesses the ability to inhibit the enzyme AchE. The enzyme AChE lowers acetylcholine levels in the brain. Inhibition of AChE therefore increases brain levels of acetylcholine.

Claims 1, 21 and 22 are believed to be adequately representative of the appealed subject matter and are reproduced below for a more facile understanding of appellants' invention.

Claim 1. A compound of the formula

wherein

R^{1} is hydrogen, (**C**$_{1}$-**C**$_{12}$)alkylcarbonyl, (**C**$_{1}$-**C**$_{12}$)alkoxycarbonyl, mono(**C**$_{1}$-**C**$_{12}$)alkylaminocarbonyl,

or di(**C**$_{1}$-**C**$_{12}$)alkylaminocarbonyl;

R^{2} is mono(**C**$_{1}$-**C**$_{18}$)alkylaminocarbonyloxy, di(**C**$_{1}$-**C**$_{8}$)alkylaminocarbonyloxy, or aryl(**C**$_{1}$-**C**$_{4}$)alkylaminocarbonyloxy;

R^{3} is hydrogen or halo; or a pharmaceutically acceptable acid addition salt thereof.

Claim 21. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an acetylcholinesterase inhibiting amount of the compound of Claim 1.

Claim 22. A method of treating memory dysfunction characterized by decreased cholinergic function which comprises administering to a mammal an

acetylcholinesterase inhibiting amount of the compound of Claim 1.

RELATED APPEALS

On page 3, lines 1 through 8 of their brief, appellants direct our attention to two, related appeals which, according to appellants, relate to the same issues as herein involved. The related appeals involve U.S. Application Serial Number 08/137,440, filed on October 15, 1993 (Appeal Number 1997-2188); and U.S. Application Serial Number 08/137,444, filed on October 15, 1993 (Appeal Number 1997-2167).

The claims in this application differ from the claims in the two related applications chiefly in the description of the substituent $\mathbf{R^2}$. Decisions in the two related appeals were mailed on even date with this opinion.

THE REJECTIONS

Claims 1 through 22 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds the specification fails to adequately teach how to use the claimed invention[2].

OPINION

We have carefully considered the entire record before us,

[2] The examiner has dropped the rejection of the same claims under 35 U.S.C. § 101 as lacking practical utility.

including the well-argued positions taken by both the examiner and the appellants. We find, however, that the examiner has failed to make out a *prima facie* case of unpatentability under the relevant statute as said statute has been interpreted by our reviewing courts. Accordingly, for reasons expressed fully below, we shall reverse the examiner's stated rejection.

THE CLAIMS

Our analysis of the issues before us begins with a determination of the scope and content of what appellants claim as their invention. As claims pending in a yet to be patented application, we must give the claims their broadest, reasonable interpretation, consistent with appellants' disclosure as said disclosure would have been understood by a person of ordinary skill in the art at the time appellants made their invention, but without importing limitations from the specification into the claims for the purpose of narrowing the scope of the claims.

The compound claims (claims 1 through 20) are directed solely to a specific group of compounds. The specific group of compounds is defined solely by the substitutents $\mathbf{R^1}$, $\mathbf{R^2}$ and $\mathbf{R^3}$ located at the various positions found on the compound

depicted by formula (II) in claim 1 and also includes the "pharmaceutically acceptable addition salts" thereof. The terminology "pharmaceutically acceptable addition salts" is conventional language used to describe well-known groups of compounds (salts) prepared from various acids and the claimed compounds. The salts are usually prepared for purposes of solubility and bioavailability. See appellants' disclosure at page 7, lines 22 through 25 for acids useful for preparing the claimed salts.

Appellants' composition claim is a so-called "comprising" claim and, as such, is directed to compositions including the recited carrier and an acetylcholinesterase inhibiting amount of the compounds defined by claim 1. The compositions are open to the inclusion of compounds such as those described by appellants in their specification at page 7, line 26 through page 9, line 10. The compositions do not exclude any other materials, including materials disclosed but not claimed and materials neither disclosed nor even contemplated.

Appellants' method claim is directed to treating memory dysfunction characterized by decreased cholinergic function by administering the compounds of claim 1 to a mammal in an amount effective to inhibit AchE. Thus, the claimed method is

limited to "treating" memory dysfunction characterized by decreased cholinergic function.

The method requires administering to a mammal with memory dysfunction characterized by decreased cholinergic function an amount of the compound of claim 1 sufficient to inhibit the formation in the mammal of the enzyme AchE. As a "comprising" claim the method does not exclude any other step or ingredient, including steps or ingredients disclosed but not claimed and even steps or ingredients neither disclosed or even contemplated.

THE "HOW TO USE" REJECTION UNDER § 112

As we have noted above, the examiner, on page 1 of his Answer, has dropped the rejection of claims 1 through 22 under 35 U.S.C. § 101. Accordingly, the only issue presented for our consideration is the rejection of claims 1 through 22 under 35 U.S.C. § 112, first paragraph.

The examiner's rejection of the claims as being based on a specification which fails to adequately teach "how to use" the claimed invention is a rejection under the so-called "enablement" requirement of the first paragraph of 35 U.S.C. § 112. It is incumbent upon the examiner in rejecting claims under the first paragraph of 35 U.S.C. § 112, to establish a

prima facie case of lack of enablement. In re Strahilevitz, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982); In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976); In re Armbruster, 512 F.2d 676, 677, 678, 185 USPQ 152, 153 (CCPA 1975); In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Moreover, in determining whether or not a disclosure is enabling, it has been consistently held that the enablement requirement of the first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. In re Marzocchi, 439 F.2d at 223, 169 USPQ at 369. In meeting the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. Marzocchi at 439 F.2d 223, 169 USPQ 369. A

specification is considered to be enabling if a person of ordinary skill in the art could "make and use" the claimed invention without resort to "undue experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

"Whether making and using an invention would have required undue experimentation, and thus, whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1 (1994), is a legal conclusion based upon underlying factual inquiries." Johns Hopkins University v. CellPro Inc., 152 F.3d 1342, 1354, 47 USPQ2d 1705, 1713 (Fed. Cir. 1998). Nevertheless, there must be a reasonable correlation between the scope of what is claimed and the scope of enablement provided by appellants' specification to the person of ordinary skill in the art. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Factors to be considered in determining whether a disclosure would require "undue" experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the

routineer in the art, (7) the predictability or lack thereof in the art, and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The examiner's position as stated in his Answer is that he considers appellants' claims to be directed to the treatment of Alzheimer's disease, the only disease mentioned in their specification as including as a symptom thereof memory loss due to decreased cholinergic function and that "undue" experimentation would be required by the person of ordinary skill in the art to practice the claimed invention. The examiner explains that appellants have failed to present adequately reliable information in their disclosure for effectively treating Alzheimer's disease. Specifically, the examiner questions the reliability of appellants' screening method for screening prospective drug candidates for treatment of memory dysfunction characterized by decreased cholinergic function. The examiner also questions whether appellants' use of the Dark Avoidance Test[3] can reliably predict efficacy in humans of the claimed compounds.

[3] See page 6, line 27 through page 7, line 15 of the specification for an explanation of the Dark Avoidance Test.

At page 2 of his Answer, the examiner has listed various prior art references which serve as the evidence which supports his rejection. Of all the listed prior art the examiner has proffered as evidence in support of his rejection, we find the article by Han et al. in the European Journal of Medical Chemistry to be the most relevant reference to the issues presented for our determination. Han et al. acknowledges on page 673 that:

> One of the more promising palliative approaches relates to potentiating the activity of the central cholinergic system. A decrease in central nervous system cholinergic markers is the most consistent and well-documented neurochemical change in Alzheimer's disease. Accordingly, several pharmacological strategies to enhance central cholinergic function are being explored: muscarinic agonists, acetylcholine releasing agents and cholinesterase inhibitors. [cites to the bibliography omitted]

Thereafter in the paragraph bridging pages 673 and 674, the authors observe that:

> Galanthamine (**1**, scheme 1), a long-acting, centrally-active competitive cholinesterase inhibitor, has shown considerable promise. This natural product, an alkaloid of the *Amaryllidaceae* family, is hydrolysis-resistant, only moderately toxic, and more readily absorbed than physostigmine. The animal data suggest that this compound might be effective in treating the central cholinergic deficits in Alzheimer's disease. A recent clinical trial found that **1** was a well-tolerated drug during long term

treatment. [cites to the bibliography omitted][4]

On page 674 the parent compound **1** and nine other galanthamine derivatives are set forth. On page 679 in Table III, the $\mathbf{IC_{50}}$'s for seven galanthamine derivatives is set forth and *in vivo* studies were conducted on galanthamine n-butyl carbamate in mice and yielded "promising results".

Additionally, the examiner has cited several other references in support of his rejection which acknowledge the role of AChE inhibitors in treating Alzheimer's disease. See for example, Robinson et al. at page 1127 wherein the authors acknowledge the therapeutic effect of AChE inhibitors for treating Alzheimer's disease. The examiner has also cited Sarter et al. as evidence that there was a recognition in the art at the time appellants made their invention that the high number of failures in clinical trials for drugs ("recognition enhancers") screened and then tested on an animal model was directly correlated to the lack of sufficient attention to the specific psychological mechanisms underlying behavioral

[4] Whether or not the results of the clinical trial have been published and whether, if published, the results are prior art having a bearing on the patentability of the appealed claims is an issue the examiner and appellants should investigate upon return of this application to the examining group.

enhancement. Nevertheless, Sarter et al. do recognize at page 154 that, "[a]rguably the strongest case for positive effects can be made for the AChE inhibitors," and Sarter et al. also observe at page 149 that:

> AChE inhibitors and muscarinic agonists can reverse behavioral deficits caused by lesions to the cholinergic basal forebrain nuclei or drug induced ACh depletion in a wide variety of learning and memory tasks. (citation omitted)

Further, both Nordberg et al. and Liston et al. recognize the mechanism by which Tacrine[5] functions is believed to be due to AChE inhibition. Indeed, Liston et al. comment that they:

> conclude that the inhibition of brain AChE by THA is sufficient to explain its <u>therapeutic</u> action in Alzheimer's disease. (emphasis ours)

Simply stated, the examiner has failed to present objective evidence sufficient to cast doubt on the objective truthfulness of appellants' assertions made in their specification and on which they rely for enablement. It is only <u>after</u> the examiner presents evidence which establishes that one of ordinary skill in the art would reasonably doubt the assertions made by appellants in their specification in support of the enablement requirement of the statute that

[5] 1,2,3,4 -tetrahydro-9-aminoacridine, also known as THA.

appellants must rebut the position taken by the examiner.

As we have noted above, on balance, the evidence on which the examiner has relied gives credence to the objective truthfulness of appellants' representations rather than casts doubt on them. Moreover, the examiner has improperly narrowly construed appellants' claims as limited to the treatment of Alzheimer's disease. Both the claims and appellants' disclosure are directed generally to treating a type of memory dysfunction in mammals characterized by decreased cholinergic function. The very art on which the examiner relies suggests that at the time appellants made their invention, AChE inhibitors were generally recognized as a class of compounds suitable for treating illness attributable to decreased acetylcholine function, including Alzheimer's disease.

The examiner also expresses his belief that the prior art on which he has relied establishes that there was, at the time of appellants' invention, no known cure or even treatment for Alzheimer's disease. In the first instance, as we have stated above, appellants do not claim either a cure of or even treatment for Alzheimer's disease but claim a method for treating a specific type of memory dysfunction. Secondly, the operative claim term used is "treating" by administration of

the claimed compounds to a mammal. We consider the term "treatment" to encompass a method which results in the mitigation of any symptom of the condition being treated but not to encompass "curing" the condition. We also disagree with the examiner's position that a method of treating a disease or medical condition must address the underlying disease or condition. Persons who suffer from allergies such as hayfever, for example, "treat" their symptoms with antihistamines and, yet, still have the underlying allergy.

Appellants' specification describes how to synthesize the claimed galanthamine compounds (see page 3, line 11 through page 5, line 17 of the specification), including eighteen examples of the synthesis of compounds within the claims (pages 10 through 23 of the specification). Appellants disclose how the claimed compounds may be administered, what constitutes effective quantities for administration and the form in which the compounds may be administered (page 7, line 26 through page 9, line 11 of the specification). Possessed of this disclosure, we have no doubt but that the skilled routineer would be able to prepare and use the claimed compounds in the manner disclosed above, without resort to "undue" experimentation.

The examiner's criticism of the claims as set forth in the statement of his rationale for rejecting the claims appears to be an expression of his concern that the claimed compounds and method of using the same may not be efficacious or even work at all. While the examiner's concern is laudable, it is misplaced here. As the court observed in In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995):

> The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See* Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)

Simply stated, approval of the Food and Drug Administration is not a prerequisite for finding a compound useful within the meaning of 35 U.S.C. § 112, first paragraph. Only objective enablement is required.

To the extent the position taken by the examiner is that appellants' claims may include inoperative embodiments we observe that it has been held that, even assuming it could be established that the claims do embrace some inoperative embodiments, it is not the function of the claims to specifically exclude all possible inoperative substances or

ineffective amounts and proportions. See, Atlas Powder Co. v. E.I. Du Pont de Nemours & Co, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984) citing In re Dinh-Nguyen, 492 F.2d 856, 858, 859, 181 USPQ 46, 48 (CCPA 1974). Accordingly, for all the above reasons, we reverse the rejection of claims 1 through 52 under 35 U.S.C. § 112, first paragraph.

SUMMARY

The rejection of claims 1 through 22 under 35 U.S.C. § 112, first paragraph, is **reversed**.

The decision of the examiner is **reversed**.

REVERSED.

SHERMAN D. WINTERS Administrative Patent Judge	)
WILLIAM F. SMITH Administrative Patent Judge	)BOARD OF PATENT) APPEALS AND)INTERFERENCES

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